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A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure

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Background. Acute renal failure (ARF) requiring dialysis in critically ill patients is associated with an in-hospital mortality rate of 50 to 80%. The worldwide standard for renal replacement therapy is intermittent hemodialysis (IHD). Continuous hemodialysis and hemofiltration techniques have recently emerged as alternative modalities. These two therapies have not been directly compared.

Methods. A multicenter, randomized, controlled trial was conducted comparing two dialysis modalities (IHD vs. continuous hemodiafiltration) for the treatment of ARF in the intensive care unit (ICU). One hundred sixty-six patients were randomized. Principal outcome measures were ICU and hospital mortality, length of stay, and recovery of renal function.

Results. Using intention-to-treat analysis, the overall ICU and in-hospital mortalities were 50.6 and 56.6%, respectively. Continuous therapy was associated with an increase in ICU (59.5 vs. 41.5%, $P < 0.02$) and in-hospital (65.5 vs. 47.6%, $P < 0.02$) mortality relative to intermittent dialysis. Median ICU length of stay from the time of nephrology consultation was 16.5 days, and complete recovery of renal function was observed in 34.9% of patients, with no significant group differences. Despite randomization, there were significant differences between the groups in several covariates independently associated with mortality, including gender, hepatic failure, APACHE II and III scores, and the number of failed organ systems, in each instance biased in favor of the intermittent dialysis group. Using logistic regression to adjust for the imbalances in group assignment, the odds of death associated with continuous therapy was 1.3 (95% CI, 0.6 to 2.7, P = NS). A detailed investigation of the randomization process failed to explain the marked differences in patient assignment.

Conclusions. A randomized controlled trial of alternative dialysis modalities in ARF is feasible. Despite the potential advantages of continuous techniques, this study provides no evidence of a survival benefit of continuous hemodiafiltration compared with IHD. This study did not control for other major clinical decisions or other supportive management strategies that are widely variable (for example, nutrition support, hemodynamic support, timing of initiation, and dose of dialysis) and might materially influence outcomes in ARF. Standardization of several aspects of care or extremely large sample sizes will be required to answer optimally the questions originally posed by this investigation.

Key words: hemodialysis, dialysis modalities, CAPD, continuous hemodiafiltration, renal replacement therapy, intensive care.

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Despite advances in intensive care unit (ICU) and dialytic technology over the past four decades, mortality rates associated with acute renal failure (ARF) remain distressingly high. Depending on the etiology of ARF and comorbid conditions, in-hospital mortality rates range from approximately 30% in nephrotoxic drug-induced ARF to 90% or more when ARF is accompanied by respiratory, hepatic, or other organ system failure [1–4]. The worldwide standard of care for ARF requiring dialysis in the ICU is intermittent hemodialysis (IHD). Continuous hemodialysis, hemofiltration, and hemodiafiltration techniques [hereafter termed continuous renal replacement therapies (CRRT)] have recently emerged as alternative dialytic modalities for critically ill patients with severe ARF.

To date, published comparisons of CRRT and IHD have shown favorable trends in survival, improved control of volume overload and azotemia, and greater hemodynamic stability with CRRT, although most have compared CRRT in centers with extensive experience to historical controls [5–8]. No direct controlled comparisons have been made between these two therapies.

To establish a valid comparison between dialytic therapies, a randomized controlled trial was designed with the following major goals: (*1*) to determine which dialytic modality was superior in terms of ICU and in-hospital survival, length of stay (LOS), and ultimate recovery of renal function; and (*2*) to determine the relative influence of comorbid conditions and severity of illness on out-

comes in ARF. The sample size was determined based on the hypothesis that CRRT would result in a reduction in ICU mortality for ARF requiring dialysis from 70 to 50% with two-tailed $\alpha = 0.05$ and $1\text{-}\beta = 0.80$.

METHODS

Study subjects

We considered all adult ICU patients with ARF in whom a nephrology service consultation was obtained at four academic medical centers in Southern California (University of California, San Diego; U.S. Naval Medical Center, San Diego; Veterans Administration Medical Center, San Diego; and University of California, Irvine, CA, USA) between January 1991 and September 1995. ARF was defined using standard laboratory parameters. For patients with no prior history of kidney disease or available laboratory values, ARF was defined by a blood urea nitrogen (BUN) ≥40 mg/dL (140 μmol/L) or a serum creatinine of ≥2.0 mg/dL (177 μmol/L). For patients with available baseline laboratory values, ARF was defined by a sustained rise in serum creatinine of ≥1 mg/dL (88.4 μmol/L) compared with baseline. Patients were deemed to have pre-existing chronic renal insufficiency (CRI) if they had a baseline creatinine of ≥2.0 mg%. A patient was considered for enrollment if in the judgment of the treating nephrologist he or she required dialysis and if the mean arterial blood pressure was >70 mm Hg with or without pressor support in the eight hours preceding randomization. Exclusion criteria included previous dialysis for acute or chronic renal failure, kidney transplantation, ARF from urinary tract obstruction, or a volume-responsive prerenal state. Indications for dialysis were similar at all four centers and included uremia, electrolyte abnormality, diuretic unresponsive fluid overload, acid-base imbalance, and a marked catabolic state, for example, burns. Informed consent was obtained from all study participants or their next of kin. The study was approved by the institutional review boards of all participating hospitals. Patients were followed prospectively from the time of initial nephrology service consultation through hospital discharge.

Treatment assignments

Patients at each center were randomized to IHD or CRRT with the intervention assignment generated by a computerized random number generator with separate lists at each center. Dialysis treatment was initiated in all patients by the consulting nephrologist. IHD was performed using ultrafiltration-controlled machines, heparin anticoagulation, bicarbonate-based dialysate, dialysate flow rates of 500 mL/min, and blood flow rates of 200 to 300 mL/min using temporary dual-lumen catheters. Cellulosic (cuprophan, cellulose acetate) and noncellulosic (polysulfone, polymethylmethacrylate, and polyacrylonitrile) membranes were employed in IHD patients. The duration of IHD treatments was determined by the nephrologist based on an estimate of the catabolic state, and ranged from three to four hours. Fluid removal per session was prescribed on an evaluation of fluid status with an aim to optimize fluid balance. When available, estimates of fluid balance were guided by central venous pressure or pulmonary capillary wedge pressures.

Hemodiafiltration (hemodialysis + hemofiltration) was prescribed for all patients in the CRRT arm. During the first two years of the study, continuous arteriovenous hemodiafiltration (CAVHDF) with arteriovenous access (single-lumen catheters placed in the femoral artery and a central vein) was performed. Thereafter, continuous venovenous hemodiafiltration (CVVHDF) was prescribed, using one of two available pump-driven devices (Hospal BSM-22 pump; Hospal Inc., Lyon, France; and Baxter BM-11; Baxter Inc., McGaw Park, IL, USA) and a dual-lumen intravenous catheter. Hemodiafiltration was accomplished using polysulfone or polyacrylonitrile membranes, blood flow rates of 100 mL/min, dialysate flow rates of 16.7 mL/min (1 L/hour), and ultrafiltration rates of 400 to 800 mL/hour. The desired fluid balance was maintained by administration of an hourly infusion rate of replacement fluid given prefilter. Systemic heparin, regional citrate, or saline flushes were variably employed for anticoagulation in CRRT, depending on the treating physician's judgment and hospital protocol. Patients were permitted to cross over from one therapy to the other based on the following criteria: (*1*) lack of adequate arterial vascular access for CAVHDF (CRRT to IHD), (*2*) intolerance of the procedure (inability to perform an adequate dialysis treatment because of intradialytic hypotension despite use of fluid boluses and pressors; IHD to CRRT), (*3*) need for mobility (requirement for patient to be out of bed in a chair; CRRT to IHD), or (*4*) transfer from the ICU (CRRT to IHD). As the duration of dialysis was variable, an adequate trial of therapy was defined as a minimum exposure of 25 hours for CRRT and two treatments of three hours or more of duration each for IHD.

Clinical data

Baseline vital signs, hemodynamic, and laboratory data were recorded for the first ICU day (most extreme values) and every day (every 12 hours) from the time of nephrology consultation. Serial Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores were computed for each day in the ICU to assess change in severity of illness [9, 10]. We determined the number of organ systems in failure (OSF) based on a modification of the criteria of Seneff and Knaus [10]. The criteria used for each OSF [11] are described in the **Appendix**.

Definitions

The primary outcome measure was all-cause ICU mortality. In-hospital mortality, ICU and hospital LOS, and recovery of renal function were secondary outcome measures. Complete recovery of renal function was defined as the return of serum creatinine to <2.0 mg/dL (177 μmol/L) or return to baseline creatinine concentration for patients with acute on chronic renal disease. Recovery was deemed to be partial when the above conditions were not met, but the patient was no longer dialysis dependent. Etiology of ARF was classified as ischemic acute tubular necrosis (ATN), nephrotoxic ATN, multisystem disorder, or uncertain.

Statistical analysis

All data were entered into PC!Info (Retriever Data Systems, Seattle, WA, USA) and converted into SAS (SAS Institute, Cary, NC, USA) data sets for analysis. Means of continuous data were compared with the Student *t* test. Categorical variables were compared with the χ^2 goodness-of-fit and Maentel-Haenszel χ^2 test for trend. Multivariable stepwise logistic-regression analysis was performed to adjust for the intergroup imbalance in explanatory variables. The primary analyses used the intent-to-treat population. Prespecified subgroup analyses were restricted to (*1*) patients who completed an adequate trial of therapy and (*2*) patients who crossed over from one treatment to another. Two-tailed *P* values <0.05 were considered statistically significant.

RESULTS

Study participants and randomization

At the four centers participating in the trial, 718 patients were consulted on for 746 episodes of ARF and 374 patients were dialyzed. Of these, 166 (44.4%) were randomized. Of the 208 non-randomized patients who received dialysis, 78 (20.9%) did not meet the hemodynamic eligibility criteria. Thirty (8.0%) were refused entry into the study by the treating physician. Fifty-two (13.9%) were not enrolled at the discretion of the consulting nephrologist. Sixteen (4.3%) refused directly or via the next of kin. Ten (2.7%) lacked an arterial access for CAVHDF, and 22 (5.9%) were enrolled in another study or did not participate for other miscellaneous reasons. We were able to ascertain the reasons for nonenrollment in 77 of the 82 patients excluded by the physicians. Reasons for nonenrollment by the participating physicians included (*1*) emergent indication for dialysis ($P = 60$), that is, marked hyperkalemia ($N = 7$), acidosis ($N = 3$), uremic complications ($N = 18$), and volume overload ($N = 19$); (*2*) specific request of transplant surgeons for heart, lung, and liver transplant patients ($N = 7$); and (*3*) other reasons ($N = 10$), that is, risk of hypotension ($N = 3$), concurrent enrollment in other ICU protocols ($N = 2$), lack of familiarity with study procedures ($N = 3$), and unsuitable patient for social reasons ($N = 2$). The 82 patients who were excluded by the physicians were further compared with those who were randomized, and no significant differences were seen at the time of consultation in the key demographic variables shown in Table 1 (data not shown). The 166 randomized patients enrolled are included in the analyses presented here. Of the 166 patients randomized, 82 were assigned to IHD and 84 were assigned to CRRT. In the CRRT arm, the majority (84.5%) of patients were treated with pumped systems (CVVHDF). Figure 1 shows the breakdown of all randomized patients enrolled in the trial. No patients were lost from the trial because of incomplete follow-up. Fourteen patients received no treatment after randomization (CRRT 11 vs. IHD 3, $P < 0.05$) because of an improvement in renal function in seven patients and death in seven patients before dialytic therapy was started. Twenty-one (12.7%) patients did not meet the criteria outlined for an adequate trial of therapy. The reasons for a limited treatment time were improvement in renal function in 9 patients and death in 12 patients (six in each group). Therefore, 35 (21.1%) patients failed to complete the trial (no treatment + limited treatment groups). Thirty-two (19.3%) patients crossed over from one therapy to the other, 15 from IHD to CRRT and 17 from CRRT to IHD. Table 1 compares the baseline clinical characteristics of the two treatment groups. De-

Table 1. Characteristics of patients at randomization

	IHD	CRRT	*P* value
N patients	82	84	
Demographics			
Mean age *years*	56.3	54.5	NS
% Male	68.3	83.3	<.023
% White	53.7	58.3	NS
% Surgical	31.7	23.8	NS
% ARF on CRF	31.7	23.8	NS
% Oliguric	24.4	20.2	NS
% Ventilated	56.7	64.1	NS
% DNR before consult	1.2	7.1	NS
% ARF 1st ICU day	42.7	45.2	NS
Etiology of ARF			
% Ischemic	53.7	53.6	NS
% Nephrotoxic	14.6	17.9	NS
% Multisystem/GN	7.3	7.1	NS
% Unknown	24.4	21.4	NS
Severity of illness scores			
% Liver failure	29.3	42.9	<.05
APACHE II	23.7	25.5	NS
APACHE III	87.7	96.4	<.045
N organs systems failing	3	3.2	NS
Renal function markers			
Urine output *L/24 h*	0.93	0.88	NS
BUN *mg/dL*	78.5	87.1	NS
Creatinine *mg/dL*	4.6	4.4	NS

Abbreviations are: IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; ARF, acute renal failure; CRF, chronic renal failure; DNR, do not resuscitate; ICU, intensive care unit; GN, glomerulonephritis; BUN, blood urea nitrogen; NS, not significant.

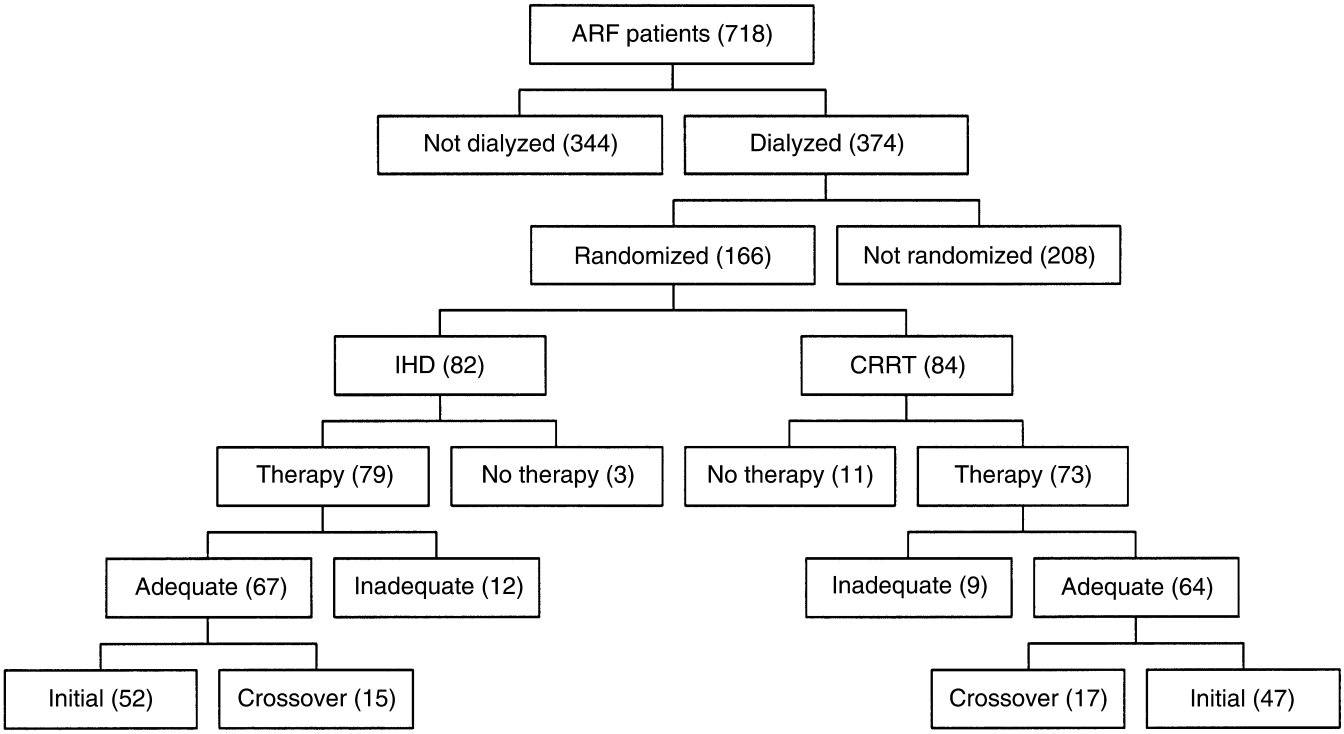

Fig. 1. Study enrollment pattern and distribution of randomized patients at each center.

spite randomization, there were significant differences in several key explanatory variables, including the proportion of men (83.3% in CRRT vs. 68.3% in IHD, $P = 0.02$) and the proportion with hepatic failure (42.9% in CRRT vs. 29.3% in IHD, $P < 0.05$). There were trends in the three severity-of-illness measures, all of which suggested that patients assigned to CRRT were in fact sicker: mean APACHE II (25.5 in CRRT vs. 23.7 in IHD, $P < 0.08$) and APACHE III (96.4 in CRRT vs. 87.7 in IHD, $P < 0.045$) score, and the mean number of failing organ systems (3.2 in CRRT vs. 3.0 in IHD, $P < 0.121$); 74.2% of the IHD group and 78.5% of the CRRT group (P = NS) were volume overloaded (defined as clinical evidence of fluid overload and fluid gain ≥4 L from baseline) at the time of initiation of dialysis. We investigated the possible reasons for these imbalances following randomization. These included (*1*) center effect, (*2*) compromised randomization, and (*3*) chance. The distribution of patients into IHD and CRRT arms was uniform at all four centers (χ^2, P = NS), and there were large differences in APACHE III scores between the CRRT and IHD groups at three of the four centers, although none were statistically different due to small sample size. There were three possible reasons for a failure of randomization: (*1*) improper random sequence generation, (*2*) inadequate allocation concealment, and (*3*) problematic implementation. We investigated each of these possibilities. The randomization sequence was generated by computer and a large block size ($N = 10$) was used. There were separate lists generated for each center. Each center had the allocation in sealed opaque envelopes through which the assignment was not visible. The master list of random assignment was kept only at the statistician's home. Additionally, there were multiple physicians involved in the study at each center so that no single physician or other provider had the opportunity of knowing (or guessing) what was the next patient's assignment. Finally, we carried out an analysis of the sequence of enrollment of all persons in relationship to those who were randomized. There was no evidence that eligible patients were systematically withheld from randomization in preference for either of the two protocols. Implementation of the randomization assignment was also uniform for all patients. There was no discrepancy in assignments stated on the randomization lists and the initial therapy given to the patient. These internal investigations indicate that randomization was not compromised. Therefore, the observed differences in patient characteristics by treatment assignment are most likely different by chance alone.

ICU and in-hospital mortality

In the intent-to-treat population, overall ICU and in-hospital mortality was 50.6 and 56.6%, respectively, well below levels typically reported in the literature. On unadjusted analysis, 28 day all cause and ICU mortality were

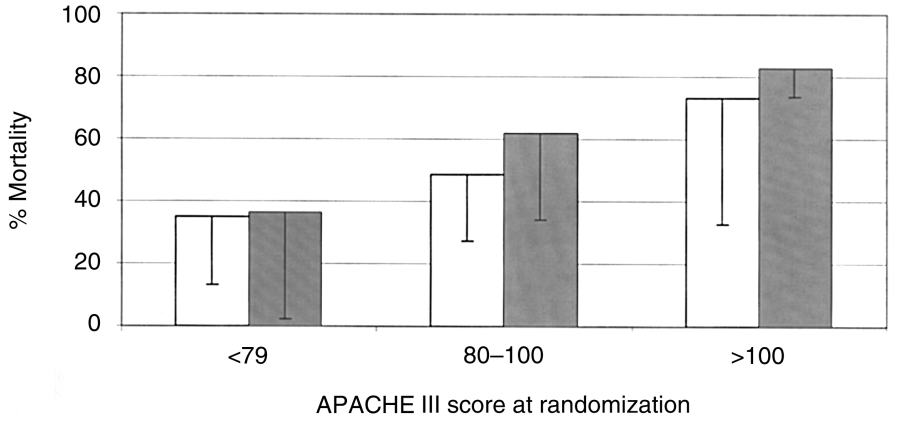

Fig. 2. Effect of severity of illness on mortality in the intermittent hemodialysis (□) and continuous renal replacement therapy (■) groups.

similar and were significantly increased with CRRT compared with IHD (59.5 vs. 41.5%, $P < 0.02$), as was in-hospital mortality (65.5 vs. 47.6%, CRRT vs. IHD, $P < 0.02$). Results were similar when the analysis was restricted to patients who had received adequate trial of therapy (ICU mortality 60.9 vs. 41.8%, CRRT vs. IHD, $P < 0.028$; hospital mortality 65.6 vs. 49.3%, CRRT vs. IHD, $P = 0.058$). When evaluating prespecified subgroups, ICU and hospital mortality were 28.9 and 38.5%, respectively, for the patients who only received IHD versus 68.1 and 72.3% for those who were treated with CRRT alone ($P < 0.001$ for both ICU and hospital mortality). In contrast, patients who crossed over from IHD to CRRT had the highest mortality rates (ICU and hospital 86.7%) in comparison to those who crossed over from CRRT to IHD (ICU 41.2% and hospital mortality 47.1%; $P < 0.02$).

Table 2. CRRT versus IHD for ARF: Prediction of ICU mortality

Variable	Parameter	*N*	% ICU mortality	OR	CI	*P*
Gender	Female	40	40	1.00	—	—
	Male	126	54	1.63	0.65–4.13	NS
Liver failure	No	106	35.9	1.00	—	—
	Yes	60	76.7	2.34	1.003–5.46	0.049
APACHE III	≤79	65	26.2	1.00	—	—
	80–100	44	47.7	1.82	0.75–4.43	NS
	>100	57	80.7	3.46	1.23–9.70	0.019
OSF	1–2	59	25.4	1.00	—	—
	3	51	47.1	1.95	0.80–4.74	NS
	≥4	56	80.4	3.40	1.15–10.09	0.027
Group	IHD	82	41.5	1.00	—	—
	CRRT	84	59.5	1.58	0.74–3.35	NS

Abbreviations are in Table 1 and: OSF, organ system failure; OR, odds ratio; CI, confidence interval.

Comorbid conditions and severity of illness

Since there were significant differences in patient characteristics between the two groups, we evaluated the associations of these characteristics with ICU and in-hospital mortality. Men were more likely to die during the study than women (54 vs. 40%, $P < 0.054$), as were patients with hepatic failure (76.4 vs. 35.1% in patients without hepatic failure, $P < 0.05$). When patients were stratified by ranking into tertiles based on their APACHE III scores at the time of randomization, ICU and in-hospital mortality were directly related to the degree of severity of illness. A similar trend was observed when patients were stratified based on the OSF score at the time of randomization. In a further evaluation of the association of severity of illness with mortality within the CRRT and IHD groups, within each stratum of APACHE III scores there was no significant difference in mortality between CRRT and IHD (Fig. 2).

Multivariable analysis

As the differences in patient characteristics and severity of illness appeared to be major determinants of mortality, the relative contribution of each of these variables was evaluated in a multivariable stepwise logistic-regression analysis, including group assignment as an independent explanatory variable. Hepatic failure, APACHE III scores, and the OSF score were independently related to ICU mortality (Table 2). Gender and hepatic failure were correlated; men were twice as likely to have hepatic failure as women, although the difference did not reach statistical significance (χ^2, $P = 0.10$). Randomization to CRRT or IHD was not independently associated with mortality after adjustment for these unbalanced covariates, suggesting that the differences in mortality observed between CRRT and IHD could be attributable to comorbidity and severity of illness, rather than dialysis modality. Indeed, the adjusted odds of death associated with CRRT was 1.58 (95% CI 0.7 to 3.3). A time-to-event analysis was conducted using proportional hazards (Cox) regression. Using this alternative method, there was a significant increase in the hazard ratio, or unadjusted relative risk of death associated with CRRT (hazard ratio 1.64, CI, 1.08 to 2.48, $P < 0.02$). Again, adjustment by APACHE III and other variables yielded the same conclusions (hazard ratio 1.35, CI, 0.89 to 2.06, $P = 0.16$).

Renal recovery

Overall, 36.6% patients (70.7% of those who survived) had a complete recovery of renal function, and there was no difference between the two groups (34.9% in CRRT vs. 33.3% in IHD, P = NS). Using an intention-to-treat analysis, 17% of patients assigned to IHD and 4% of those assigned to CRRT were left with CRI ($P = 0.01$) at hospital discharge or death. There was no significant difference in the frequency of CRI in the ARF versus ARF on CRI groups within each therapy assignment. Of the surviving patients, 7% in the IHD and 14% in the CRRT group (P = NS) remained on maintenance dialysis at hospital discharge. However, continuous therapy was associated with a significantly higher rate of complete renal recovery in surviving patients who received an adequate trial of therapy with no crossover (CRRT 92.3% vs. IHD 59.4%, $P < 0.01$). In addition, patients who crossed over from CRRT to IHD had a significantly higher rate of complete recovery than those crossing over from IHD to CRRT (CRRT to IHD 44.7% vs. IHD to CRRT 6.7%, $P < 0.01$). Severity of illness was an important determinant of renal recovery. The lowest rates of renal recovery were observed among patients with APACHE III scores >100 (60.7% vs. 50.0% vs. 25.0% for APACHE III scores ≤79, 80 to 100 and >100, respectively, $P < 0.001$). Similar findings were seen with increasing APACHE II and OSF scores. Finally, renal recovery was rare in patients who died.

Length of stay

As the timing of nephrology consultation and patient enrollment into the study varied in relationship to the patient's admission to the hospital and ICU, the LOS was calculated from the time of randomization. ICU LOS was similar in both groups using an intent-to-treat analysis (CRRT 15.1 vs. IHD 16.7 days, P = NS). Hospital LOS was significantly reduced for patients who received CRRT as the initial therapy only (CRRT 17.1 vs. IHD 26.3 days, $P < 0.01$). This difference in part may be related to the higher ICU mortality rate observed in the CRRT arm. Patients who received both therapies had longer ICU and hospital lengths of stay. Higher APACHE III and OSF scores were associated with shorter LOS, reflecting higher mortality rates with higher scores. Similarly, survivors had longer ICU lengths of stay than nonsurvivors.

Control of azotemia and volume overload

Using an intention to treat analysis of the 166 randomized patients, we found that the total number of treatments was slightly lower in the group assigned to CRRT (8.07) than in the group assigned to IHD (8.67), although the difference is not statistically significant ($P = 0.75$). As some patients in each group crossed over, 82 patients assigned to IHD averaged 5.25 IHD treatments and 7.0 CRRT treatments (for the 15 crossover patients) per person per week. The 84 patients assigned to CRRT averaged 5.34 IHD treatments (for the 17 crossover patients) and 6.94 CRRT treatments per person per week. The mean duration of each IHD (3.1 hours) and CRRT treatment (16.1 hours) was similar in the two groups. Technical efficacy of the two modalities was assessed by evaluating the BUN and creatinine concentrations at various time points following initiation of dialysis. It is evident that the nature of IHD results in alternate peaks and troughs of solute levels depending upon the frequency of dialysis, while CRRT is associated with a steady state level of solutes [12]. A comparison of mean daily BUN and creatinine levels between the two groups from the first dialysis treatment for the first 10 days is shown in Figure 3. Continuous therapy resulted in lower solute levels despite higher mean BUN values at the start of therapy. Mean dialyzer BUN clearance was 21.5 mL/min in patients treated with CRRT. Predialysis and post-dialysis BUN levels were not routinely available to compute urea reduction ratios or Kt/V in the IHD patients. The efficacy of volume control in the two arms was compared by evaluating the cumulative fluid balance in each patient. Since CRRT techniques have an inherent advantage in this regard, we additionally assessed the ability of each protocol to achieve the stated goal for fluid removal. More than one fourth (28.8%) of the IHD treatments were unable to achieve the stated fluid goals. It is difficult to assess a similar parameter for CRRT, since the duration of CRRT typically far exceeds that of IHD, and short-term ultrafiltration goals are less well-defined. Fewer than 1 in 10 (9%) CRRT treatments fell short of the desired ultrafiltration goal.

Technical complications

Data were accumulated on the incidence of technical complications related to access, anticoagulation, and pump use. For CRRT techniques, we distinguished between arteriovenous techniques (CAVHDF) and venovenous techniques (CVVHDF) as the access and driving forces are different. Arterial access was difficult to obtain in 3 out of 32 patients with CAVHDF and required multiple attempts. Difficulties in obtaining venous access were encountered in 5.3% cases of CAVHDF, 6.1% IHD, and 9.5% in CVVHDF. Arterial access clotting was seen in 0.3% of all cases, while venous access clotting was more frequent and occurred in 1.5% of all cases, and was equally frequent in the CRRT and IHD techniques. Tubing disconnection was seen in 0.2% of IHD and 0.3% of CRRT. Blood loss >50 mL attributable to the procedure occurred in 0.25 of IHD and 6.3% of CVVHDF procedures. Membrane leaks were seen in 0.2% of CVVHDF, 0.9% of CAVHDF techniques, and were not observed in IHD. Restricting the analysis to

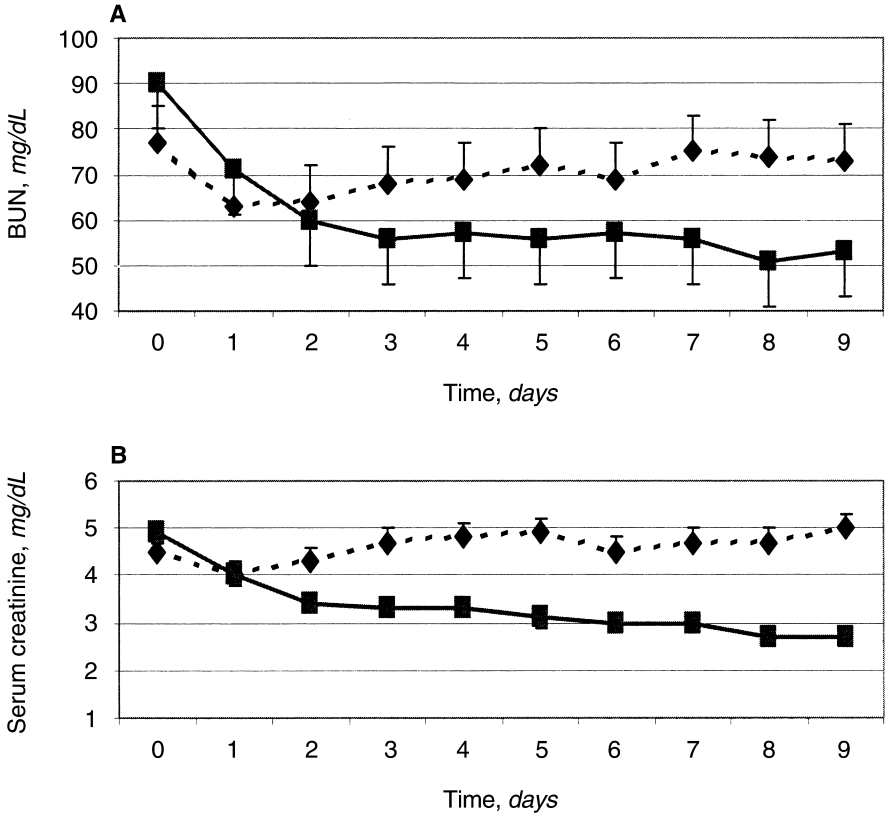

Fig. 3. Control of blood urea nitrogen (BUN) (*A*) and serum creatinine (*B*) during therapy with IHD(◆) and CRRT(■).

patients who only received IHD or CRRT (excluding crossovers), 0.8% of the IHD group and 1.9% of the CRRT group (P = NS) developed bleeding complications. One percent of the heparin anticoagulated IHD runs (N = 205) versus 9.4% of heparin anticoagulated CRRT days (N = 85) were complicated by bleeding (systemic or localized associated with high PTT >150 sec). All the bleeding complications were seen in heparin CAVHDF procedures. None of the citrate anticoagulated IHD (N = 26) or CRRT days (N = 284) had any episodes of bleeding, while 0.7% of the saline anticoagulated IHD (N = 129), and none of the saline flush CRRT (N = 62) had bleeding complications. Metabolic complications were more common in CRRT than IHD: hypernatremia (defined as Na >145; IHD 12.0% vs. CRRT 22.0%, $P < 0.001$) and alkalemia (pH 7.44 and bicarbonate >28; IHD 9.8% vs. CRRT 15.6%, $P < 0.02$). Hypernatremia was more common in patients on saline flush or citrate anticoagulation (saline IHD 15.8% vs. saline CRRT 21.4, P = NS; citrate IHD 11.1% vs. citrate CRRT 26.8%, P = NS). Alkalemia was most commonly seen in citrate anticoagulated procedures (citrate IHD 29.6% vs. citrate CRRT 18.8%, P = NS), but was also present in patients on heparin and saline flush anticoagulation. The incidence of hypernatremia was similar in CAVHDF (18.8%) and CVVHDF (23.0%, P = NS) procedures, while alkalemia was more common with CAVHDF (21.2%) than CVVHDF (14.1%, P = NS).

Costs

Resource utilization per treatment day was calculated to determine the labor costs (by prospectively documenting the time spent by nurses, technicians, physicians, N = 449) and material costs (equipment, disposables, solutions, N = 1352). Material costs were significantly higher for CRRT ($338) than that for IHD ($66) with the major contributor for CRRT being the dialysate (33% of total cost) followed by the cost of the filters (20%) and the rental costs of infusion pumps (20%). The labor costs for IHD ($216) and CRRT ($205) were similar. The total direct cost per treatment was much higher for CRRT ($543) compared with IHD ($282); the overall cost of dialysis also was affected by the number of treatments. The total direct cost of dialysis was affected by both the cost per treatment and the number of treatments received. Using an intention-to-treat analysis of the 166 randomized patients, the total number of treatments was slightly lower in the group assigned to CRRT (7.9) than in the group assigned to IHD (8.4), although the difference was not statistically significant (P = 0.77). Some patients in each group crossed over, 82 patients assigned to IHD averaged 5.8 IHD treatments and 2.6 CRRT treatments per person. The 84 patients assigned to CRRT averaged 1.3 IHD treatments and 6.6 CRRT treatments per person. Total per patient treatment costs for CRRT were $3946 and $3077 for IHD ($P$ = NS).

DISCUSSION

Contemporary management of ARF requiring dialysis in the ICU includes a decision regarding the choice of dialysis modality, including IHD, peritoneal dialysis, and continuous hemodialysis, hemofiltration, and hemodiafiltration. This study was designed to assess whether the type of dialysis modality (CRRT or IHD) used to treat ARF in the ICU setting affects mortality, length of stay, and the likelihood of recovery of renal function. We hypothesized that CRRT would be superior to IHD and designed the trial to detect a 27% difference in ICU mortality.

The data show an overall mortality rate of 50.6%, considerably lower than the 60 to 80% rates reported in most published studies. This finding may be due to the clinical trial effect reflecting an improved level of care or may reflect the exclusion of patients too ill (hypotensive) to be randomized [13]. ICU mortality was 59.5% with CRRT and 41.5% with IHD, a statistically significant and clinically important difference. On the surface, these findings support a survival advantage for IHD, although further analysis provides an alternate explanation. It is well recognized that severity of illness affects disease-specific outcomes in critically ill patients. In this study, each of three indices of severity of illness (APACHE II and III and OSF) and two other clinical factors significantly associated with mortality (male gender and hepatic failure) were not evenly distributed, with more severe nonrenal disease present in the patients randomized to CRRT [14, 15]. A detailed investigation failed to reveal any specific factors accounting for these differences. A logistic regression analysis adjusting for these factors yielded a nonsignificant difference by treatment assignment. Furthermore, within strata of APACHE II and III scores, the relative mortality rates of CRRT and IHD were not significantly different. Additionally, survival analysis of time to outcome (data not shown) did not reveal any significant difference between the two modalities. This pattern was apparent even when patients who did not receive any therapy in either group were excluded from the analysis. Together these findings strongly suggest that the increased risk of death observed in the CRRT group was the direct result of nonrenal disease and that no definite statement can be made regarding the superiority of one modality or the other.

In our study, patients who crossed over from IHD to CRRT had an increase in their APACHE and OSF scores at the time of crossover, while those who crossed over to IHD from CRRT had a decrease in their scores (data not shown). These findings also highlight the importance of severity of illness and likely explain the phenomenon described previously in this article among crossover patients. Indeed, a change from CRRT to IHD represents a complex array of events that may include transfer out of intensive care, improved hemodynamic stability, and resolution of volume overload.

It may be unrealistic to assume that a single decision in the complex care of a critically ill patient could significantly influence survival. Mortality in the critically ill patient is likely to be influenced by several factors unrelated to dialysis. It has been previously shown that the do-not-resuscitate (DNR) status in the ICU setting influences the level of care administered and the eventual outcome [16]. We found that 7.1% of CRRT and 1.2% of IHD patients (P = NS) were made DNR prior to nephrology consultation. A perception of futility, among other factors, may affect practice and reduce the effectiveness of any intervention. It also should be noted that other dialysis-related factors were not controlled for, including the timing of initiation, frequency, intensity, membrane choice, and dose of dialysis [17]. Although membrane choice has been variably shown to affect outcome from ARF in recent studies, it is unlikely that membrane played a significant role in this study as all the CRRT patients and the majority of IHD patients were treated with synthetic, noncellulosic membranes. Of course, a myriad of other conditions and their treatments (for example, antibiotics, pressor agents, nutrition support) also may limit the specificity of an intervention such as a change in dialysis modality. Swartz et al have recently validated this viewpoint based on a retrospective comparison of CVVH versus IHD at a single center [18]. Using a Cox proportional hazards model, they showed that the sickest patients are more likely to receive CRRT as initial therapy and the underlying comorbidities account for the difference in mortality observed in their patients.

Mortality is an important outcome, although it may not be the most appropriate primary outcome for ARF, for many of the reasons cited previously in this article. Recovery of renal function and the need for short- and long-term dialysis may be more specific outcome measures to evaluate in the patient with ARF [19, 20]. Renal recovery was rare in patients who died; however, survivors had varying levels of recovery of renal function, and this appeared to be related to modality. Complete recovery of renal function was achieved more frequently in patients on CRRT compared with IHD. The mechanism for this finding is unknown, but clearly warrants further study. Intermittent dialysis may be associated with more frequent hemodynamic insults [21]. Alternatively, improved control of azotemia, clearance of middle molecules [22], and reduction in pulmonary, myocardial, gastrointestinal, and other tissue edema may also play a role.

Technical complications were similar in both groups and were largely related to anticoagulant use. Despite the longer exposure to CRRT techniques, the overall frequency of complications was similar in the two groups. Although the daily cost for CRRT is more than that for

IHD, the difference in costs is largely related to the increased expense of materials. At the time this study was done, CRRT was not as widely used as it is today, and the cost of materials has changed. Additionally, how many filter kits are used can largely influence the costs for CRRT. As CRRT techniques gain wider acceptance and methods to promote filter life are more universally adapted, it is likely that this difference in overall costs will be significantly reduced.

This study provides important information on trial design and the difficulties in carrying out an interventional trial for dialysis in the ICU setting. Although the implementation of the study from start to follow-up was sound, randomization was not effective at reducing bias in treatment assignment. The study was powered to detect a difference of 27% (50 vs. baseline 70%) in ICU mortality. This approach failed to account for trial-related reductions in the mortality rate of the group receiving standard care (IHD). Had the study been larger in number, the power to detect a difference between modalities would have been greater, and the study would have been less likely to have experienced unbalanced randomization due to chance. It could be argued that selection of patients excluded the majority of available patients because of hemodynamic instability or physician choice. However, our analysis shows that the patients excluded by the physician's choice were not significantly different than those enrolled. CRRT is most commonly reserved for patients who are unable to receive IHD, and we had designed the protocol to exclude patients with MAP <70 to avoid bias against IHD. CRRT is probably the most beneficial in patients who are hemodynamically unstable; however, it is difficult to design a study that enrolls only this group of patients. Additionally, the wide variation in practice of indications for and timing of initiation of dialysis is a major limitation. Standardization of dialytic and nondialytic management might have improved specificity for the intervention. However, there is no worldwide agreement on most aspects of ARF management, including significant fundamental decision points, such as the optimal timing of initiation, frequency, membrane, and dose of dialysis. Indeed, much of ARF practice has resulted from extrapolation from the end-stage renal disease setting and has never been validated [23].

In summary, our study proved that a randomized controlled trial in critically ill patients with ARF is feasible. While overall mortality was lower than reported previously, unadjusted results showed an increase in ICU and in-hospital mortality among patients treated with CRRT, although this difference was best explained by more severe illness in the CRRT group, despite randomization. Complete recovery of renal function was more common in patients assigned to the CRRT arm. This study did not control for other major clinical decisions or other supportive management strategies that are widely variable (for example, nutrition support, hemodynamic support, timing of initiation, and dose of dialysis) and might materially influence outcomes in ARF. Standardization of several aspects of care and a significantly larger sample will be required to answer optimally the questions originally posed by this investigation.

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APPENDIX

Criteria for organ system failure

Cardiovascular. Heart rate ≤54 per min, mean arterial blood pressure ≤49 mm Hg, occurrence of ventricular tachycardia and/or ventricular fibrillation or other cardiac arrhythmias requiring continuous infusion of antiarrhythmic, requirement for temporary pacemaker, intra-aortic balloon pump or ventricular assist devices.

Neurological. Glasgow coma score (GCS) ≤6. When sedatives were used, these were recorded.

Renal. Blood urea nitrogen (BUN) ≤40 mg/100 mL or creatinine ≥2.0 mg/100 mL for patients with no previous history of renal disease, an increase in creatinine >1 mg% for patients with pre-existing renal disease.

Hematological. White blood cells (WBC) ≤1000 mm^3, platelets ≤20,000 mm^3, hematocrit ≤20% (not chronic renal failure), requirement for platelet transfusions to maintain platelet levels >20,000/mm^3.

Respiratory. Respiratory rate ≤5/min or ≥49/min, $Paco_2$ ≥50 mm Hg, $AaDo_2$ ≥350 mm Hg, ventilator dependent after 24 hours of OSF.

Liver. Clinical acute liver failure with elevations in bilirubin levels (total and direct); aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP), greater than two times normal. Additionally, an increase in prothrombin time and INR of >1.5. For patients with pre-existing chronic liver disease, documented evidence of worsened liver function and presence of encephalopathy.

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